B1

1. (Amended) A sustained-release pharmaceutical composition for an ionic prostanoic acid derivative comprising an prostanoic acid derivative and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative, which increases the oil/water partition coefficient of the ionic prostanoic acid derivative.

2. (Amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic compound having an opposite charge to the ionic prostanoic acid derivative, which increases the oil/water partition coefficient of the ionic prostanoic acid derivative, contains a hydrophobic group in the molecule thereof.

Please add the following new claims 17 and 18:

B2

--17. (New) A sustained-release pharmaceutical composition for a cationic ionic prostanoic acid derivative comprising an prostanoic acid derivative and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative and increasing hydrophobicity of the prostanoic acid derivative, wherein said ionic compound contains a carboxyl, sulfate, sulfonate or phosphate group in the molecule thereof, or a salt thereof.

18. (New) A sustained-release pharmaceutical composition according to claim 17, wherein the ionic compound is sodium lauryl sulfate and/or sodium oleate.--

REMARKS

Claims 1-18 are pending in this application. Claim 5 has been canceled without prejudice or disclaimer. Claims 1 and 2 have been amended. Claims 17 and 18 are newly presented. No new matter has been introduced with the foregoing amendments and new claims. The claims as pending are reproduced in the Appendix for the Examiner's convenience. Attached hereto is a marked-up version of the changes made to

the claims by the current amendment. The attached page is captioned "Version with markings to show changes made." Reconsideration is respectfully requested.

I. THE INVENTION

The present invention is directed to a sustained-release pharmaceutical composition containing an ionic prostanoic acid derivative, and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative. The ionic compound is capable of enhancing the hydrophobic property of the ionic prostanoic acid derivative. Unexpectedly, these ionic complexes exhibit an excellent sustained release effect.

II. SUPPORT FOR THE AMENDMENTS TO THE CLAIMS AND NEWLY ADDED CLAIMS

Amendments to claims 1 and 2 finds support, for example, in claim 5. Claims 17 and 18 find support, for example, in claims 1, 14 and 15. The Examiner indicated that claims 14 and 15 would be allowable if rewritten in independent form. Applicants have rewritten these claims in independent form. As such, Applicants believe claims 17 and 18 are in condition for allowance.

III. REJECTION UNDER 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-13, and 16 under 35 U.S.C. § 103(a) as allegedly being obvious over JP 02262519 ("JP '519") in view of Monaghan *et al.* ("WO 9857972"). The Examiner states that JP '519 discloses an agent comprising a prostaglandin I_2 derivative as an ammonium salt. The Examiner alleges that Monaghan *et al.* teach an ammonium compound to treat nerve conditions associated with diabetes. The Examiner alleges that it would have been obvious to combine the teachings of JP '519 with Monaghan *et al.* due the similar structure and activity. In response, Applicants respectfully traverse the rejection.

> As set forth in M.P.E.P. § 2143, "[t]o establish a *prima facie* case of obviousness, *three* basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the references; 2) there is no reasonable expectation of success; and 3) the references do not teach or suggest all the claim limitations.

1. There is no Suggestion or Motivation to Modify the References

Applicants state that there is simply no motivation or suggestion provided in the cited references to modify their teaching in the way the Examiner has contemplated. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The invention disclosed in JP-'519 is directed to a second use of beraprost, that is, a therapeutic use of beraprost for nervous disorders caused by diabetes. As disclosed therein, an active ingredient ammonium salt of beraprost can be produced

according to the method described in JP-A-58-1 24778, Paragraph 1, in the Example. However, this reference merely discloses this ammonium salt as a ***single component***.

JP-'519 does not teach or suggest a sustained-release pharmaceutical composition containing two components *i.e.*, 1) an ionic prostanoic acid derivative, and 2) an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative and capable of enhancing the hydrophobic property of the ionic prostanoic acid derivative.

Monaghan *et al.* do not supply the deficiencies of the primary reference. Monaghan *et al.* teach quaternary ammonium compounds useful as dual NK_1 and NK_2 receptor antagonists and can therefore be used for treating an inflammatory disease such as arthritis, psoriasis, asthma or inflammatory bowel disease, a central nervous system (CNS) disorder such as anxiety, depression, dementia or psychosis, a gastrointestinal (GI) disorder such as functional bowel disease, as well as other indications. There is no teaching or suggestion of making a sustained released composition using the ionic complexes of the present invention.

In stark contrast to the cited art, the present invention is directed to a sustained-release pharmaceutical composition containing an ionic prostanoic acid derivative, and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative and capable of enhancing the hydrophobic property of the ionic prostanoic acid derivative.

Further, as set forth on page 6, lines 7-15 of the English translated specification, the pharmaceutical compositions of the present invention, especially those having large partition coefficients have sustained release effects, are far superior to the prostanoic acid derivatives alone.

An excellent sustained release composition is obtained by increasing the hydrophobicity of the prostanoic acid derivative, by for example, chlorinating the body of the active compound with a paired ion by virtue of an electrostatic effect. The ionic compound is capable of enhancing the hydrophobic property of the ionic prostanoic acid

derivative. Unexpectedly, these ionic complexes exhibit an excellent sustained release effect.

As such, there is simply no motivation or suggestion provided in the cited references to modify their teaching in the way the Examiner has contemplated. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

2. There is No Reasonable Expectation of Success

In addition, there is no reasonable expectation of success that the modification that the Examiner contemplates will succeed. Applicants assert that there is absolutely no teaching or suggestion in JP-'519 to modify the teaching therein to arrive at the presently claimed invention. There is no reasonable expectation that the modification that the Examiner contemplates will succeed. Neither JP-'519, nor Monaghan *et al.* teach or suggest a sustained-release pharmaceutical composition containing an ionic prostanoic acid derivative, and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative and capable of enhancing the hydrophobic property of the ionic prostanoic acid derivative. Advantageously, the ionic compound is capable of enhancing the hydrophobic property of the ionic prostanoic acid derivative.

Thus, the Examiner has used hindsight reconstruction of the cited art in an attempt to piece together the present invention. Hindsight reconstruction is impermissible and therefore, Applicants respectively request that the Examiner withdraw the rejection.

3. The references do not teach or suggest all the claim limitations

Finally, the references do not teach or suggest all of the claim limitations. The present invention claims a method for obtaining a sustained-release pharmaceutical composition by increasing the oil/water partition coefficient of the ionic prostanoic acid derivative active compound, by chlorinating the body of the ionic active compound with a paired ion by virtue of the electrostatic effect, thereby the oil/water partition coefficient

thereof can be increased, without modifying chemically the body of the ionic active compound.

In contrast, JP-'519 and Monaghan *et al.* merely disclose that the body of an ionic active compound is chlorinated with an ionic compound having an opposite charge. However, neither JP-'519, nor Monaghan *et al.* teach or suggest the chlorination of the body of the ionic active compound with a paired ion by virtue of the electrostatic effect, thereby the oil/water partition coefficient thereof can be increased, without modifying chemically the body of the ionic active compound.

In the case of the method disclosed in the '972, the hydrophobicity of the compound is controlled by introducing an alkyl group and the like as a side chain into the body of the quaternary ammonium active compound having a high water solubility in the form of covalent binding. Thus, the present invention is entirely irrelevant to the '972.

As such, Applicants respectfully request that the Examiner withdraw the rejection.

IV. OBJECTIVE EVIDENCE REBUTS ANY *PRIMA FACIE* CASE OF OBVIOUSNESS

Applicants can rebut a *prima facie* case of obviousness by presenting comparative test data showing that the claimed invention possesses unexpectedly improved properties or properties that the prior art does not possess. *In re Dillion*, 16 U.S.P.Q. 1897, 1901 (Fed. Cir. 1990).

Applicants maintain that a *prima facie* case of obviousness has not been established. However, the comparative data filed with the application rebuts any *prima facie* case of obviousness. The Examiner's attention is respectfully directed to Table 1 on pages 24-25 of the disclosure. As shown therein, an increase in the partition coefficient of the ionic prostanoic acid derivative was noted with alkylbenzylammonium salts such as tributylbenzylammonium chloride, alkyltrimethylammonium salts such as lauryltrimethylammonium chloride, lidocaine hydrochloride and meprylcaine

hydrochloride. Results reveal that the compounds having opposite charges such as quaternary ammonium or phosphonium groups and highly hydrophobic substituents exhibit the effect of increasing the hydrophobic property of the ionic prostanoic acid derivative (*see*, page 25, lines 24 -28 of the specification).

However, inorganic salts such as magnesium chloride or arginine hydrochloride, failed to enhance the hydrophobic property of beraprost sodium (BPS) (*see*, page 23, lines 19-23). Thus, no increase in the partition coefficient was noted.

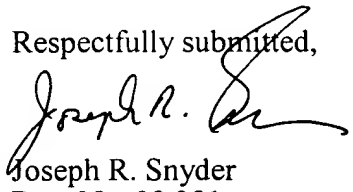
Further, the Examiner attention is respectfully directed to page 29, bridging to page 30 and Figure 3. As explained in Test 5, inventive Example 17 and comparative Example 4 were administered to Winstar rats. As shown in Figure 3, the inventive composition 17 (closed circles) showed a sustained released compared to the comparative Example 4 (open squares). Thus, the compositions as presently claimed produce unexpectedly improved properties for controlled release. These unexpected advantageous properties represent objective evidence sufficient to rebut a *prima facie* case of obviousness. Accordingly, the Examiner is respectfully requested to withdraw the 35 U.S.C. §103(a) rejection.

V. CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



Joseph R. Snyder
Reg. No. 39,381

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (415) 576-0200
Fax: (415) 576-0300
JS:mys
WC 9041683 v1

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claim 5 has been canceled without prejudice or disclaimer.

Claims 1 and 2 have been amended in the following manner:

1. (Amended) A sustained-release pharmaceutical composition for an ionic prostanoic acid derivative comprising an prostanoic acid derivative and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative ,which increases the oil/water partition coefficient of the ionic [and increasing hydrophobicity of the] prostanoic acid derivative.

2. (Amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic compound having an opposite charge to the ionic prostanoic acid derivative [and increasing] ,which increases the oil/water partition coefficient of the ionic [hydrophobic property of the] prostanoic acid derivative, contains a hydrophobic group in the molecule thereof.

Please add claims 17-18:

17. (New) A sustained-release pharmaceutical composition for a cationic ionic prostanoic acid derivative comprising an prostanoic acid derivative and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative and increasing hydrophobicity of the prostanoic acid derivative, wherein said ionic compound contains a carboxyl, sulfate, sulfonate or phosphate group in the molecule thereof, or a salt thereof.

18 (New) A sustained-release pharmaceutical composition according to claim 17, wherein the ionic compound is sodium lauryl sulfate and/or sodium oleate.

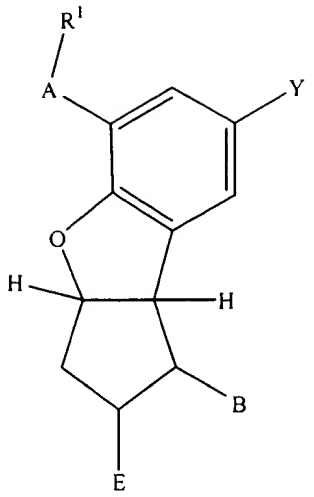
APPENDIX

1. (Amended) A sustained-release pharmaceutical composition for an ionic prostanoic acid derivative comprising an prostanoic acid derivative and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative and increasing the oil/water partition coefficient of the ionic prostanoic acid derivative.

2. (Amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic compound having an opposite charge to the ionic prostanoic acid derivative and increasing the oil/water partition coefficient of the ionic prostanoic acid derivative contains a hydrophobic group in the molecule thereof.

3. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic prostanoic acid derivative is a prostaglandin I_2 derivative.

4. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic prostaglandin I_2 derivative is a compound represented by the following general formula (I):



wherein R^1 represents $COOR^2$ (wherein R^2 represents:

1) hydrogen or a pharmacologically acceptable cation,

2) $-Z-Ar^1$, wherein Z is a valence bond or a straight or branched alkylene shown by C_tH_{2t} wherein t is an integer of 1 to 6, and Ar^1 is 2-pyridyl, 3-pyridyl or 4-pyridyl;

3) $-C_tH_{2t}COOR^3$, wherein C_tH_{2t} has the same significance as defined above, and R^3 is hydrogen or a pharmacologically acceptable cation;

or,

4) $-C_tH_{2t}N(R^4)_2$, wherein C_tH_{2t} has the same significance as defined above, and R^4 is hydrogen, a straight alkyl having 1 to 12 carbon atoms or a branched alkyl having 3 to 14 carbon atoms);

A represents:

1) $-(CH_2)_m-$, wherein m is an integer of 1 to 3;

2) $-CH=CH-CH_2$;

3) $-CH_2-CH=CH-$;

4) $-CH_2-O-CH_2-$;

5) $-CH=CH-$;

6) $-O-CH_2-$; or,

7) C≡C-;

Y represents hydrogen, an alkyl having 1 to 4 carbon atoms, chlorine, bromine, fluorine, formyl, methoxy or nitro;

B represents -X-$C(R^5)(R^6)OR^7$ (wherein R^5 represents hydrogen or an alkyl having 1 to 4 carbon atoms; R^7 represents hydrogen, an acyl having 1 to 14 carbon atoms, an aroyl having 6 to 15 carbon atoms, tetrahydropyranyl, tetrahydrofuranyl, 1-ethoxyethyl or t-butyl; X represents:

1) $-CH_2-CH_2-$;

2) -CH=CH-;or

3) -C≡C-;

R^6 represents:

1) a straight alkyl having 1 to 12 carbon atoms or a branched alkyl having 3 to 14 carbon atoms;

2) -Z-Ar^2 wherein Z has the same significance as defined above and Ar^2 is phenyl, α-naphthyl, β-naphthyl or a phenyl substituted with at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl, an alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy;

3) $-C_tH_{2t}OR^8$, wherein C_tH_{2t} has the same significance as defined above, and R^8 is a straight alkyl having 1 to 6 carbon atoms, a branched alkyl having 3 to 6 carbon atoms, phenyl, a phenyl substituted with at least one of chlorine, bromine, fluorine, iodine, trifluoromethyl, an alkyl having 1 to 4 carbon atoms, nitro, cyano, methoxy, phenyl or phenoxy, cyclopentyl, cyclohexyl, or a cyclopentyl or cyclohexyl substituted with 1 to 4 straight alkyl group(s) having 1 to 4 carbon atoms;

4) -Z-R^9, wherein Z has the same significance as defined above, and R^9 is hydrogen, a cycloalkyl having 3 to 12 carbon atoms or a substituted cycloalkyl having 3 to 12 carbon atom which is substituted with 1 to 3 alkyl groups having 1 to 5 carbon atoms;

5) $-C_tH_{2t}-CH=C(R^{10})R^{11}$, wherein C_tH_{2t} has the same significance as defined above, and R^{10} and R^{11} represent hydrogen, methyl, ethyl, propyl or butyl; or

6) $-C_uH_{2u}-C\equiv C-R^{12}$, wherein u is an integer of 1 to 7, C_uH_{2u} is a straight or branched alkylene and R^{12} is a straight alkyl having 1 to 6 carbon atoms);

E represents hydrogen or OR^{13}, wherein R^{13} is hydrogen, an acyl having 1 to 12 carbon atoms, an aroyl having 7 to 18 carbon atoms, a straight alkyl having 1 to 12 carbon atoms or a branched alkyl having 3 to 14 carbon atoms; or a salt thereof.

5. (Canceled)

6. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic compound is incorporated at least in an equimolar amount based on the ionic prostanoic acid derivative in terms of a charge ratio.

7. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic prostanoic acid derivative is anionic.

8. A sustained-release pharmaceutical composition according to claim 7, wherein the ionic compound is a compound containing a group selected from an ammonium, pyridinium, phosphonium and sulfonium group in the molecule thereof, or a salt thereof.

9. A sustained-release pharmaceutical composition according to claim 8, wherein the ionic compound contains at least one member selected from the group consisting of an alkyldimethylbenzylammonium salt, an alkyltrimethylammonium salt, an alkylpyridinium salt, an alkylamine salt and an alkylphosphonium salt.

10. A sustained-release pharmaceutical composition according to claim 9, wherein the ionic compound is benzalkonium chloride.

11. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic prostanoic acid derivative is a synthetic ionic prostanoic acid derivative.

12. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the prostaglandin I_2 derivative is (±)-(1R*-2R*, 3aS*, 8bS*)-2,3,3a,8b-tetrahydro-2-hydroxy-1-[(E)-(3D*)-3-hydroxy-4-methyl-1-octen-6-ynyl]-1H-cyclopenta[b]benzofuran-5-butanoic acid, or a salt thereof.

13. (Previously amended) A sustained-release pharmaceutical composition according to claim 1, wherein the ionic prostanoic acid derivative is cationic.

14. A sustained-release pharmaceutical composition according to claim 13, wherein the ionic compound is a compound containing a carboxyl, sulfate, sulfonate or phosphate group in the molecule thereof, or a salt thereof.

15. A sustained-release pharmaceutical composition according to claim 14, wherein the ionic compound is sodium lauryl sulfate and/or sodium oleate.

16. (Previously amended) A sustained-release pharmaceutical composition according to claim 13, wherein the ionic prostanoic acid derivative is a synthetic ionic prostanoic acid derivative.

17. (New) A sustained-release pharmaceutical composition for a cationic ionic prostanoic acid derivative comprising an prostanoic acid derivative and an ionic compound having an opposite charge to that of the ionic prostanoic acid derivative and increasing hydrophobicity of the prostanoic acid derivative, wherein said ionic compound contains a carboxyl, sulfate, sulfonate or phosphate group in the molecule thereof, or a salt thereof.

18 (New) A sustained-release pharmaceutical composition according to claim 17, wherein the ionic compound is sodium lauryl sulfate and/or sodium oleate.